

WEST Search History

DATE: Thursday, April 29, 2004

| Hide? | <u>Set</u> <u>Name</u> | <u>Query</u> | <u>Hit</u> <u>Count</u> |
|--------------------------|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| | | <i>DB=PGPB,USPT; PLUR=YES; OP=ADJ</i> | |
| <input type="checkbox"/> | L17 | L16 and l10 | 40 |
| <input type="checkbox"/> | L16 | 20011206 | 58 |
| <input type="checkbox"/> | L15 | L14 and (dna or cdna or nucleic acid or polynucleotide or nucleotide or vector or plasmid) | 102 |
| <input type="checkbox"/> | L14 | L13 and (mak\$7 or synthe\$7 or produ\$7 or ferment\$7 or cultur\$7) | 106 |
| <input type="checkbox"/> | L13 | L12 and microorganism | 106 |
| <input type="checkbox"/> | L12 | L11 and mevalonate | 176 |
| <input type="checkbox"/> | L11 | (isopentenyl pyrophosphate) or (Isopentenyl diphosphate) or (methyl pyrophosphate) or (methyl trihydrogen pyrophosphate) or (butenyl pyrophosphate) | 372 |
| <input type="checkbox"/> | L10 | L9 or l8 or l7 or l6 or l5 or l4 or l3 or l2 or l1 | 30011 |
| <input type="checkbox"/> | L9 | (536/23.2)!.ccls. | 10802 |
| <input type="checkbox"/> | L8 | (435/320.1)!.ccls. | 23412 |
| <input type="checkbox"/> | L7 | (435/252.3)!.ccls. | 8102 |
| <input type="checkbox"/> | L6 | (435/232)!.ccls. | 440 |
| <input type="checkbox"/> | L5 | (435/194)!.ccls. | 1507 |
| <input type="checkbox"/> | L4 | (435/189)!.ccls. | 1204 |
| <input type="checkbox"/> | L3 | (435/183)!.ccls. | 4483 |
| <input type="checkbox"/> | L2 | (435/132)!.ccls. | 215 |
| <input type="checkbox"/> | L1 | (435/41)!.ccls. | 675 |

END OF SEARCH HISTORY

=> d his

(FILE 'HOME' ENTERED AT 09:09:11 ON 29 APR 2004)

FILE 'REGISTRY' ENTERED AT 09:09:17 ON 29 APR 2004

L1 1 S ISOPENTENYL PYROPHOSPHATE/CN
L3 257 S MEVALONATE

FILE 'HCAPLUS' ENTERED AT 09:11:41 ON 29 APR 2004

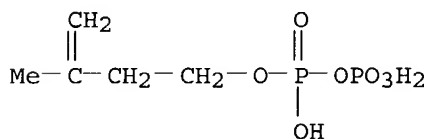
FILE 'REGISTRY' ENTERED AT 09:11:45 ON 29 APR 2004

SET SMARTSELECT ON
L4 SEL L1 1- CHEM : 5 TERMS
SET SMARTSELECT OFF

FILE 'HCAPLUS' ENTERED AT 09:11:45 ON 29 APR 2004

L5 1182 S L4
L6 8 S L5 (L) MEVALON? (L) PREP/RL
L7 6 S L6 AND PD<20011206

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 358-71-4 REGISTRY
 CN Diphosphoric acid, mono(3-methyl-3-butenyl) ester (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 3-Buten-1-ol, 3-methyl-, pyrophosphate (6CI)
 CN 3-Buten-1-ol, 3-methyl-, trihydrogen pyrophosphate (7CI, 8CI)
 OTHER NAMES:
 CN Δ3-Isopentenyl pyrophosphate
 CN 3-Methyl-3-butenyl pyrophosphate
 CN Isopentenyl diphosphate
 CN **Isopentenyl pyrophosphate**
 FS 3D CONCORD
 MF C5 H12 O7 P2
 CI COM
 LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
 BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CIN,
 CSCHEM, EMBASE, IPA, MEDLINE, NIOSHTIC, TOXCENTER, USPAT2, USPATFULL
 (*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

513 REFERENCES IN FILE CA (1907 TO DATE)
 7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 515 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 22 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L7 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:612949 HCAPLUS

DOCUMENT NUMBER: 139:226151

TITLE: Development of methodology for biochemical and biosynthetic studies of isoprenoid compounds using perdeuterated mevalonate

AUTHOR(S): Eguchi, Tadashi; Dekishima, Yasumasa; Matsushima, Yoshitaka; Tamegai, Hideyuki; Kakinuma, Katsumi; Takagi, Motoki; Kuzuyama, Tomohisa; Seto, Haruo; Misawa, Norihiko; Hamano, Yoshimitsu; Dairi, Tohru

CORPORATE SOURCE: Department of Chemistry and Materials Science, Department of Chemistry, Tokyo Institute of Technology, Japan

SOURCE: Tennen Yuki Kagobutsu Toronkai Koen Yoshishu (2001), 43rd, 7-12
CODEN: TYKYDS

PUBLISHER: Nippon Kagakkai

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Isoprenoids are chemical diverse in nature, ubiquitous in living organisms, and crucial in biol. processes. The biosynthesis of such isoprenoids proceeds through mevalonate and nonmevalonate pathways depending upon organisms and cellular organelle, isopentenyl diphosphate (IPP) being a key intermediate in both cases. Metabolic engineering and control of these pathways should thus provide new opportunity to study intriguing chemical and biochem. involved and to develop selective chemotherapeutic agents and isoprenoid-related materials. We describe a new practical approach to the preparation of highly- and multiply deuterated isoprenoids, zeaxanthin and diterpene antibiotic terpentecin being as examples, and its potential for analyzing the biosynthetic mechanism of isoprenoids, based on the metabolic engineering of microorganisms. Obviously, deuterium-labeled compds. are invaluable in biochem., bioorg. as well as physicochem. research. Metabolically engineered *E. coli* DK223 (pTMV20, pACCAR25ΔcrtX) produces zeaxanthin under the presence of mevalonate. Fully deuterated mevalonolactone-d₉ (MVL-d₉), which had been synthesized, was supplemented to the culture of the above triply-engineered *E. coli*, and the biosynthesized zeaxanthin was extracted and purified by repeated chromatog. All the zeaxanthin formed was proved to be derived only from the supplemented MVL-d₉. This was the first example of such highly and multiply deuterated zeaxanthin, and clearly demonstrated significant potential of the present approach for the preparation of various isotope-labeled isoprenoids. Addnl. example of this approach was also demonstrated in the mechanistic study of cyclization reaction in the biosynthesis of diterpene antibiotic terpentecin. Straightforward stereochem. anal. of isoprenoid biosynthesis was demonstrated by one-shot labeling of MVL-d₉ and 1H NMR spectroscopy. Precise anal. of the simplified proton spectra of highly deuterated isoprenoids, especially under the deuterium decoupled conditions, appeared to be beneficial for mechanistic enzymol., particularly, for the key transformation involving proton attack and proton quench as observed in the terpene cyclase reactions.

L7 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:435280 HCAPLUS

DOCUMENT NUMBER: 135:41836

TITLE: A gene cluster for the mevalonate pathway from *Streptomyces* sp. strain CL190 and use in isoprenoid synthesis

INVENTOR(S): Seto, Haruo; Kuzuyama, Tomohisa; Takahashi, Shunji; Takagi, Motoki

PATENT ASSIGNEE(S): Japan

SOURCE: PCT Int. Appl., 75 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|--------------------------------------------------------------------------------------------------|-----------------|--------------|
| ----- | --- | ----- | ----- | ----- |
| WO 2001042476 | A1 | 20010614 | WO 2000-JP8620 | 20001206 <-- |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| JP 2001161370 | A2 | 20010619 | JP 1999-348375 | 19991208 <-- |
| PRIORITY APPLN. INFO.: JP 1999-348375 A 19991208 | | | | |
| AB A gene cluster for the mevalonate pathway enzymes, Phosphomevalonate kinase, Diphosphomevalonate decarboxylase, Mevalonate kinase, 3-Hydroxy-3-methylglutar yl CoA reductase, and 3-Hydroxy-3-methylglutar yl CoA synthase, from Streptomyces is disclosed. Recombinant expression, and use in biosynthesis of isoprenoid compds., ubiquinone, vitamin K2, or carotenoid, are claimed. A biosynthetic 3-hydroxy-3-methylglutaryl CoA reductase (EC 1.1.1.34), the rate-limiting enzyme of the mevalonate pathway for isopentenyl diphosphate biosynthesis, had previously been purified from Streptomyces sp. strain CL190 and its corresponding gene (hmgr) had been cloned. Sequence anal. of the flanking regions of the hmgr gene revealed 5 new open reading frames, orfA to -E, which showed similarity to those encoding eukaryotic and archaebacterial enzymes for the mevalonate pathway. Feeding expts. with [1-13C]acetate demonstrated that Escherichia coli JM109 harboring the hmgr gene and these open reading frames used the mevalonate pathway under induction with iso-Pr β -D-thiogalactopyranoside. This transformant could grow in the presence of fosmidomycin, a potent and specific inhibitor of the nonmevalonate pathway, indicating that the mevalonate pathway, intrinsically absent in Escherichia coli, is operating in the E. coli transformant. The hmgr gene and orfABCDE are thus unambiguously shown to be responsible for the mevalonate pathway and to form a gene cluster in the genome of Streptomyces sp. strain CL190. Production of Isopentenyl pyrophosphate (IPP) and ubiquinone was demonstrated in transformed E. coli. | | | | |
| REFERENCE COUNT: | 5 | THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT | | |

L7 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:77831 HCAPLUS

DOCUMENT NUMBER: 135:164538

TITLE: Escherichia coli engineered to synthesize isopentenyl diphosphate and dimethylallyl diphosphate from mevalonate: a novel system for the genetic analysis of the 2-C-methyl-D-erythritol 4-phosphate pathway for isoprenoid biosynthesis

AUTHOR(S): Campos, Narciso; Rodriguez-Concepcion, Manuel; Sauret-Gueto, Susanna; Gallego, Francesca; Lois, Luisa-Maria; Boronat, Albert

CORPORATE SOURCE: Department de Bioquimica i Biologia Molecular, Facultat de Quimica, Universitat de Barcelona, Barcelona, 08028, Spain

SOURCE: Biochemical Journal (2001), 353(1), 59-67
 CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP) constitute the basic building block of isoprenoids, a family of compds. that is extraordinarily diverse in structure and function. IPP and DMAPP can be synthesized by two independent pathways: the mevalonate pathway and the recently discovered 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway. Although the MEP pathway is essential in most eubacteria, algae and plants and has enormous biotechnol. interest, only some of its steps have been determined. We devised a system suitable for the genetic anal. of the MEP pathway in *Escherichia coli*. A synthetic operon coding for yeast 5-diphosphomevalonate decarboxylase, human 5-phosphomevalonate kinase, yeast mevalonate kinase and *E. coli* isopentenyl diphosphate isomerase was incorporated in the chromosome of this bacterium. The expression of this operon allowed the synthesis of IPP and DMAPP from mevalonate added exogenously and complementation of lethal mutants of the MEP pathway. We used this system to show that the *ygbP*, *ychB* and *ygbB* genes are essential in *E. coli* and that the steps catalyzed by the products of these genes belong to the trunk line of the MEP pathway.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:911403 HCAPLUS

DOCUMENT NUMBER: 134:67159

TITLE: Mevalonate pathway genes involved in isopentenyl diphosphate biosynthesis in gram-positive cocci

INVENTOR(S): Brown, James R.; Gwynn, Michael; Mathie, Thomas B.; Myers, Joseph E., Jr.; Traini, Christopher M.; Van Horn, Stephanie; Wilding, Edwina Imogen

PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA; Smithkline Beecham P.L.C.

SOURCE: PCT Int. Appl., 158 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|----------------------------------------------------------------------------|------|----------|-----------------|--------------|
| WO 2000078935 | A1 | 20001228 | WO 2000-US17262 | 20000622 <-- |
| W: JP | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |

PRIORITY APPLN. INFO.: US 1999-140519P P 19990622

US 1999-146682P P 19990802

AB The invention provides mevalonate pathway genes from gram-pos. bacteria, encoded polypeptides, and methods for recombinant expression. Also provided are methods for utilizing mevalonate pathway genes, polypeptides, or antibodies for screening of antibacterial compds. The mevalonate pathway and the glyceraldehyde 3-phosphate (GAP)-pyruvate pathway are alternative routes for the biosynthesis of the central isoprenoid precursor, isopentenyl diphosphate. Genomic anal. revealed that the staphylococci, streptococci, and enterococci possess genes predicted to encode all of the enzymes of the mevalonate pathway and not the GAP-pyruvate pathway, unlike *Bacillus subtilis* and most gram-neg. bacteria studied, which possess only components of the latter pathway. Phylogenetic and comparative genome analyses suggest that the genes for mevalonate biosynthesis in gram-pos. cocci, which are highly divergent from those of mammals, were horizontally transferred from a primitive eukaryotic cell. Enterococci uniquely encode a bifunctional protein predicted to possess both 3-hydroxy-3-methylglutaryl CoA (HMG-CoA)

reductase and acetyl-CoA acetyltransferase activities. Genetic disruption expts. have shown that five genes encoding proteins involved in this pathway (HMG-CoA synthase, HMG-CoA reductase, mevalonate kinase, phosphomevalonate kinase, and mevalonate diphosphate decarboxylase) are essential for the in vitro growth of *Streptococcus pneumoniae* under standard conditions. Allelic replacement of the HMG-CoA synthase gene rendered the organism auxotrophic for mevalonate and severely attenuated in a murine respiratory tract infection model. The mevalonate pathway thus represents a potential antibacterial target in the low-G+C gram-pos. cocci.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1987:454274 HCAPLUS

DOCUMENT NUMBER: 107:54274

TITLE: Inhibition of cholesterol biosynthesis by fluorinated mevalonate analogs

AUTHOR(S): Reardon, John E.; Abeles, Robert H.

CORPORATE SOURCE: Grad. Dep. Biochem., Brandeis Univ., Waltham, MA, 02254, USA

SOURCE: Biochemistry (1987), 26(15), 4717-22
CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The conversion of mevalonate to cholesterol in rat liver homogenates (50% inhibitory concentration = 0.01-1.0 mM) is inhibited by 6-mono- (I), 6,6-di- (II), and 6,6,6-trifluoromevalonate (III), as well as 4,4-difluoromevalonate (IV). Addition of compound I, III, or IV to rat liver homogenates results in the accumulation of 5-phospho- and 5-pyrophosphomevalonate. The conversion of isopentenyl pyrophosphate to cholesterol is not inhibited by the fluorinated analogs. Thus, the decarboxylation of mevalonate 5-pyrophosphate is apparently inhibited. Rat liver homogenates catalyze the phosphorylation of I and III. The inhibition of the decarboxylation of mevalonate 5-pyrophosphate by I and III is demonstrated directly with partially purified decarboxylase. Compound I is a remarkably effective inhibitor of the decarboxylation ($K_i = 10$ nM). It is likely that the phosphorylated or pyrophosphorylated forms of all inhibitors tested are responsible for inhibition. A chemical method for the synthesis of mevalonate 5-pyrophosphate is also described.

L7 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1974:564916 HCAPLUS

DOCUMENT NUMBER: 81:164916

TITLE: Metabolism of mevalonic acid to phosphorylated intermediates in a cell-free extract from *Nepeta cataria* leaves

AUTHOR(S): Downing, Michael R.; Mitchell, Earl D.

CORPORATE SOURCE: Agric. Exp. Stn., Oklahoma State Univ., Stillwater, OK, USA

SOURCE: Phytochemistry (Elsevier) (1974), 13(8), 1419-21
CODEN: PYTCAS; ISSN: 0031-9422

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A cell-free extract was prepared from leaves of *N. cataria* plants which converted mevalonic acid to mevalonic acid phosphate, mevalonic acid pyrophosphate, and isopentenyl pyrophosphate. These enzymes were in the 30,000 g supernatant. The activities were maximal at pH 7 and the formation of mevalonic acid pyrophosphate and isopentenyl pyrophosphate reached a maximum after an incubation time of 180 min, whereas the level of mevalonic acid phosphate began to decrease after 90 min.